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Intracranial pressure and cerebral perfusion pressure in patients developing brain death☆

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ABSTRACT

Purpose: We investigated whether a critical rise of intracranial pressure (ICP) leading to a loss of cerebral perfusion pressure (CPP) could serve as a surrogate marker of brain death (BD).
Materials and methods: We retrospectively analyzed ICP and CPP of patients in whom BD was diagnosed (n = 32, 16-79 years). Intracranial pressure and CPP were recorded using parenchymal (n = 27) and ventricular probes (n = 5). Data were analyzed from admission until BD was diagnosed.
Results: Intracranial pressure was severely elevated (mean ± SD, 95.5 ± 9.8 mm Hg) in all patients when BD was diagnosed. In 28 patients, CPP was negative at the time of diagnosis (−8.2 ± 6.5 mm Hg). In 4 patients (12.5%), CPP was reduced but not negative. In these patients, minimal CPP was 4 to 18 mm Hg. In 1 patient, loss of CPP occurred 4 hours before apnea completed the BD syndrome.
Conclusions: Brain death was universally preceded by a severe reduction of CPP, supporting loss of cerebral perfusion as a critical step in BD development. Our data show that a negative CPP is neither sufficient nor a prerequisite to diagnose BD. In BD cases with positive CPP, we speculate that arterial blood pressure dropped below a critical closing pressure, thereby causing cessation of cerebral blood flow.

1. Introduction

Brain death (BD) is defined as the complete and irreversible loss of clinically detectable brain function. Diagnosis requires the presence of unresponsive coma, brainstem areflexia, and central apnea [1]. Despite a general agreement in intensive care medicine on the key anatomical and physiological concept of BD, there is no worldwide consensus regarding the diagnostic requirements [2,3]. In particular, BD is still surrounded by debate on how to ascertain completeness and irreversibility of the loss of brain function [2,4,5]. Although the validity of a purely clinical approach remains unrefuted [1], there may be a place for ancillary tests as surrogate markers of irreversibility of the clinical syndrome [6]. In this regard, demonstration of absent cerebral blood flow (CBF) is highly convincing because prolonged loss of blood supply to the brain inevitably causes the death of all brain neurons. In various countries, studies of cerebral perfusion using angiographic methods, brain nuclear scans, or transcranial Doppler ultrasound (TCD) are accepted as ancillary tests to confirm BD [3]. In recent years, several new computed tomography (CT)– and magnetic resonance imaging–based techniques have been proposed to study perfusion in suspected BD [7–10]. Maintaining CBF requires the presence of an adequate cerebral perfusion pressure (CPP), defined as the difference between mean arterial pressure (MAP) and intracranial pressure (ICP). Using intracranial probes, continuous monitoring of ICP, CPP, and brain tissue oxygenation has become part of the routine clinical care of patients with acute brain injuries. It has been suggested that these new diagnostic options might also contribute to BD diagnostic protocols in the future [11,12]. In a recent survey, a small number of US neurology or neurosurgery institutions reported that absent CPP has been included in their institutional guidelines for diagnosis of BD [13]. However, available data on ICP and CPP in BD are still very limited.

In the present study, we investigated ICP and CPP levels derived from an electronic patient data recording system in patients developing BD due to primary brain injuries. The underlying conditions most often lead to an immediate rise of ICP, thus threatening a critical fall of CPP. It was hypothesized that a severe reduction of CPP would represent an essential step in the development of BD. In this sample, we also investigated a potential influence of the underlying diseases on the evolution of ICP and CPP before BD. It was assumed that diseases that lead to a

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rapid increase of intracranial blood volume (eg, subarachnoid hemorrhage [SAH]) would be accompanied by a faster and more severe increase of ICP compared to brain infectious diseases or brain tumor.

Throughout this article, we use the term *the time BD was diagnosed* instead of *the time BD occurred*. As the definition of BD does not solely claim the complete loss of brain functions but also its irreversibility, all guidelines require a diagnostic workup to exclude reversibility. The very moment irreversibility is ascertained marks "the time BD is diagnosed," but the time BD actually did occur is an event of the past. By the nature of the BD definition and the process of BD diagnostics, it is impossible to precisely determine "the time BD occurs."

2. Method

A chart review was performed to identify all patients in whom BD was diagnosed between January 1, 2009, and December 31, 2013. Only patients with continuous ICP and CPP data were included in this study. Patients were treated on an interdisciplinary neurologic and neurosurgical intensive care unit located at a university hospital. Brain death was diagnosed according to current German guidelines [6]. Briefly, after exclusion of confounding factors such as sedatives, muscle relaxants, circulatory shock, hypothermia, or severe metabolic disturbances, 2 qualified physicians must independently document the presence of unresponsive coma, loss of all brainstem reflexes, and central apnea. In adults with primary supratentorial brain lesions, it is mandatory to confirm the irreversibility of the BD syndrome through re-examination of the key clinical symptoms no earlier than 12 hours after first BD examination. Alternatively, irreversibility may be established by demonstrating absent cerebral perfusion using TCD or a brain nuclear scan (ie, (99mTc-hexamethylpropylene amine oxime (HMPAO) scintigraphy), by demonstrating 30 minutes of "silent" electroencephalography (EEG), or absence of intracranial responses of somatosensory or auditory-evoked potentials.

As part of the standardized operating procedures at our institution, patients who have unconsciousness due to severe brain injury receive intracranial probes to monitor ICP and CPP. All monitoring probes were implanted before diagnostic investigations for BD. In 27 patients, ICP was monitored using probes implanted in the brain parenchyma (Neurovent P; Raumedic AG, Münchberg, Germany). In the remaining 5 cases, ICP was monitored using an externalized catheter implanted in one of the lateral ventricles (Integra Neuroscience, Andover, UK). In these respective patients, ventricle catheters showed sufficient recording with reliable ICP measurement until BD was diagnosed. Arterial blood pressure (ABP) was monitored invasively with catheters in a radial or femoral artery. Pressure levels of ICP and ABP were both zeroed at the level of the external auditory channel.

Cerebral perfusion pressure was calculated according to the formula:

$$CPP = MAP - ICP$$

Calculated CPP values may hence become negative once ICP exceeds MAP. In physiological terms, this indicates absence of net cerebral perfusion.

Intracranial pressure, MAP, and CPP values were registered using an electronic documenting system (Computer Organized Patient Report Assistant, COPRA 5; COPRA System GmbH, Berlin, Germany). Storage of the respective data occurred in intervals of 30 minutes. Intracranial pressure and CPP data were analyzed across the entire treatment course from admission until BD diagnosis. For further analysis, we averaged ICP at the time BD was diagnosed across all patients as well as maximal individual ICP levels during the time before BD confirmation. Similarly, CPP was averaged across all patients at the time BD was diagnosed as well as minimal CPP levels during the time before BD confirmation. Moreover, we determined the interval between the onset of the initial injury and the time BD diagnosis could be confirmed. Kruskal-Wallis analysis of variance was performed to identify a potential influence of the causative disease on the aforementioned parameters.

The study was approved by the *Ethics Commission–Charité–Universitätsmedizin Berlin*. Because of the retrospective design of the study that exclusively involved analysis of clinical routine data, consent of the patients or their legally authorized representatives was not necessary.

The temporal relationship between CPP changes and the stepwise manifestation of clinical BD signs was analyzed in more detail in a recent patient with high-resolution data recording (ICMplus software; University of Cambridge, Cambridge Enterprise, Cambridge, UK, http://www.neurosurg.cam.ac.uk/icmplus). Written informed consent was obtained from the patient's legal representatives for publication of his individual details and accompanying images (Fig. 4) in this manuscript.

3. Results

Inclusion criteria were met by 32 patients (age, 16-79 years; females, n = 16). Brain death was confirmed in 31 patients using ancillary testing and in 1 patient by clinical reassessment 12 hours after the first examination. EEG was used most often as ancillary test (n = 17), followed by brain nuclear scan (ie, 99mTc-HMPAO perfusion scintigraphy, n = 11) and TCD (n = 3), respectively. The most common disease causing BD was SAH (n = 12) followed by traumatic brain injury (TBI) (n = 8), malignant ischemic stroke (n = 4), spontaneous intracerebral hemorrhage (ICH) (n = 4), meningitis (n = 3), and brain tumor (n = 1).

The average time from the initial brain injury to BD diagnosis was 5.7 days (range, 1-25 days; Fig. 1). The shortest interval was seen in patients with TBI with an average of 2.8 days. However, statistical analysis between groups failed to show significant differences according to the causative diseases. A more detailed analysis of the intervals in patients with SAH suggested that 2 different pathophysiological factors influenced the development of BD within this subgroup. More than half of the SAH patients (n = 7) developed BD within the first 3 days after admission. In these patients, ICP increased irresistibly due to fulminant hemorrhages. Four patients, however, developed BD after 13 to 16 days. In these patients, cerebral vasospasm with consecutive ischemic swelling led to BD. In patients with malignant ischemic stroke, BD typically developed around day 4 after admission (range, 4-5 days).

In all patients, ICP was severely elevated at the time of BD diagnosis (Fig. 2). The respective ICP across all patients was 95.5 ± 9.8 mm Hg (mean ± SD). Intracranial pressure was often even higher in the hours before BD was confirmed with an average maximum of 108.3 mm Hg (±9.5 mm Hg). A comparison of maximal ICP values in different patient groups as defined by the respective causative diseases yielded no statistically significant differences. In all groups, the average maximal ICP before BD confirmation reached values more than 100 mm Hg (maximal ICP in patients with SAH: 114.6 ± 8.7 mm Hg; TBI: 101.3 ± 9.7 mm Hg; stroke: 100.5 ± 11.0 mm Hg; ICH: 113.3 ± 13.0 mm Hg; meningitis: 106.7 ± 8.1 mm Hg; tumor: 104.0 mm Hg). In most patients, the critical increase of ICP was accompanied by a complete absence of CPP at the time of BD examination (mean CPP ± SD, −8.2 ± 6.5 mm Hg; Fig. 2). In the hours before BD was confirmed, calculated CPP was often even lower with an average minimal CPP of −13.5 mm Hg (±6.4 mm Hg; Fig. 3). Comparing different patient groups as defined by the respective causative diseases yielded no statistically significant differences (minimal CPP in patients with SAH: −13.5 ± 7.5 mm Hg; TBI: −13.9 ± 6.4 mm Hg; stroke: −12.8 ± 9.1 mm Hg; ICH: −17.0 ± 3.0 mm Hg; meningitis: −8.3 ± 5.2 mm Hg; tumor: −16.0 mm Hg). Similarly, there were no relevant differences between patients who were monitored using parenchymal or ventricle probes (minimal CPP of patients with parenchymal probes vs ventricle probes: −13.7 ± 6.8 vs −12.6 ± 3.5 mm Hg). Mean duration of absent CPP in those patients in whom CPP turned negative was 13.1 hours (1-31 hours). In 4 patients (12.5%), CPP was also severely reduced but was not negative (Fig. 3). Minimal CPP in these patients was